(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 May 2004 (27.05.2004)

PCT

(10) International Publication Number
WO 2004/043165 A1

(51) International Patent Classification[7]: A23L 1/00, 1/22, A23P 1/04, 1/08, A61K 9/00

(21) International Application Number:
PCT/CH2003/000739

(22) International Filing Date:
12 November 2003 (12.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/426,442 14 November 2002 (14.11.2002) US
0301537.7 23 January 2003 (23.01.2003) GB

(71) Applicant *(for all designated States except US)*: GIVAUDAN SA [CH/CH]; Chemin de la Parfumerie 5, CH-1214 Vernier (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: VIRGALLITO, Margaret, T. [US/US]; 1622 Beaverbook Drive, Dayton, OH 45432 (US). ZHANG, Jing [CN/US]; 2028 Stratford Court, Loveland, OH 45140 (US).

(74) Agent: McSTEA, John, Anthony; Givaudan Schweiz AG, Global Patents, Überlandstrasse 138, CH-8600 Dübendorf (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/043165 A1

(54) Title: EDIBLE FILM CONTAINING FOOD ACID

(57) Abstract: An edible film composition for delivering an active agent to the oral cavity, the composition comprising a water-dispersible film composition comprising a cellulose ether and a starch, and a food acid.

It is highly desirable to provide films that can deliver a tartness or sourness and mouth-watering effect and which are mechanically strong and hygroscopically stable.

The applicant has now surprisingly found that by combining certain types of film-forming polymers it is possible to form edible films that rapidly dissolve or disintegrate and disperse in the mouth and which solve the problems referred to above.

Accordingly, the invention provides in a first aspect an edible film for delivering an active agent to the oral cavity comprising a water-dispersible film-forming material selected from a cellulose ether and a starch, and a food acid.

The food acid may be selected from the group consisting of citric acid, malic acid, glacial acetic acid, anthranilic acid, tartaric acid, tiglic acid, ascorbic acid, benzoic acid, tannic acid, succinic acid, adipic acid, fumaric acid and lactic acid.

These food acids, are preferably employed in edible film formulations at levels of at least about 8% by weight based on the dry weight of the edible film composition, more preferably from about 8% to about 25% by weight. Dry weight according to the present invention refers to the weight of all of the edible film composition components without added water. The above-mentioned levels of food acids are preferred in order to give a desirable tartness or sourness impression and to achieve a desirable mouth-watering effect. Whereas, it may be possible to incorporate lower amounts of acid into the films and thereby avoid any instability problems associated with the films, one cannot reliably achieve the desirable mouth-sensations aforementioned.

The acid may be incorporated into the films in encapsulated form. In this manner, high levels of acid (even higher than the amounts aforementioned if desired) may be incorporated without any detrimental effects on the physical properties of the film, however in many applications, the acid has to be released immediately into the mouth as the film disintegrates in order to provide an instant mouth-watering effect. If the acid is encapsulated, the onset of the mouth-watering effect is delayed, in a manner dependant on the release of the acid from the capsule.

formers is from 50 to 90%, more particularly 50 to 80% by weight based on the dry weight of the composition.

The ratio of cellulose ether to starch may also vary considerably depending on the disintegration properties sought. Typically one may employ 4 parts cellulose ether to 1 part starch. However, this ratio may vary. For example, if one wants to increase the rate of hydration of the film one can increase the starch content; whereas if one wants to increase the mechanical strength of the film, higher amounts of cellulose ether are preferred.

The edible film may additionally contain gelatin or pectin. Gelatin or pectin may assist in the hydration of the film when it is placed in the mouth. Rapid hydration is important to because customers often associate slow hydration with unpleasant mouth feel. It is preferred if hydration of films occurs in a matter of seconds, e.g. within 30 seconds, more particularly 5 to 10 seconds. Gelatin or pectin may be employed at levels of up to about 30 wt% based on the dry weight of the formulation.

Edible film according to the invention may contain other, optional, ingredients. For example, the film may contain excipients that assist in film formation, handling and stability such as emulsifiers and plasticisers. Other excipients may include preservatives, anti-oxidants, colourants and the like. The films may also contain additional active agents as stated above.

As emulsifiers one can mention lecithin, stearates, ester derivatives of stearates, palmitates, ester derivatives of palmitates, oleates, ester derivatives of oleates, glycerides, ester derivatives of glycerides, sucrose polyesters, polyglycerolesters, and animal waxes, vegetable waxes, synthetic waxes, petroleum , and mixtures thereof. Particularly useful emulsifiers are lecithin, non-ionic surfactants, such as polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, or polyoxyethylene castor oil derivatives with one or more polyalcohols, or mixtures thereof.

Emulsifiers may be employed in amounts of up to 2% by weight, more preferably up to 1% by weight based on the dry weight of the formulation.

Flavourants may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Representative flavor oils include: spearmint oil, cinnamon oil, peppermint oil, clove oil, bay oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, and oil of bitter almonds. Also, one can mention artificial, natural or synthetic fruit flavors such as vanilla, chocolate, coffee, cocoa and citrus oil, including lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. These flavorings can be used individually or in admixture.

Examples of suitable flavour components include without limitation 2-Methyl Pyrazine, Acetophenone Extra, Alcohol C6, Alcohol C8, Aldehyde C7 Heptylic, Aldehyde C8, Aldehyde C9, Allyl Caproate, Amyl Butyrate, Anisicaldhyde, Benzaldehyde, Benzyl Acetate, Benzyl Alcohol, Benzyl Butyrate, Benzyl Formate, Benzyl Iso Valerate, Benzyl Propionate, Butyl Acetate, Camphor, Cinnamic Aldehyde, Cis-3-Hexenol, Cis-3-Hexenyl Acetate, Cis-3-Hexenyl Formate, Cis-3-Hexenyl Propionate, Citronellal, Citronellol, Cuminic Aldehyde, Damascenone, Damascone Alpha, Damascone Beta, Diethyl Malonate, Dimethyl Anthranilate, Dimethyl Benzyl Carbinyl Acetate, Estragole, Ethyl Acetate, Ethyl Aceto Acetate, Ethyl Benzoate, Ethyl Heptoate, Ethyl Salicylate, Ethyl-2-Methyl Butyrate, Eucalyptol, Eugenol, Fenchyl Acetate, Fenchyl Alcohol, Methyl-2-octynoate, 2-sec-Butylcyclohexanone, Styralyl Acetate, Hexyl Acetate, Ionone Alpha, Iso Amyl Acetate, Iso Butyl Acetate, Iso Menthone, Jasmone Cis, Laevo Carvone, Linalool, Linalool Oxide, Melonal, Menthol, Menthone, Methyl Acetophenone, Methyl Amyl Ketone, Methyl Benzoate, Methyl Heptenone, Methyl Hexyl Ketone, Methyl Para Cresol, Methyl Phenyl Acetate, Methyl Salicylate, Neral, Nerol, Para Cresol, Para Cresyl Acetate, Para Tolyl Aldehyde, Phenyl Acetaldehyde, Phenyl Ethyl Acetate, Phenyl Ethyl Butyrate, Phenyl Ethyl Formate, Phenyl Ethyl Iso Butyrate, Phenyl Ethyl Propionate, Phenyl Propyl Acetate, Phenyl Propyl Aldehyde, 4-Methyl-2-(2-methyl-1-propenyl)tetrahydropyran, Styralyl Propionate, Terpineol, Terpinolene, Trans-2-Hexenal, Hexyl Cinnamic Aldehyde Alpha, Oxacycloheptadec-10-en-2-one, Linalyl Benzoate, Cedrol, Benzyl Cinnamate, Linalyl Cinnamate, Phenyl Ethyl Cinnamate, Para Cresyl Phenyl Acetate, Benzyl Salicylate, Hexyl Salicylate, Phenyl Ethyl Salicylate, and Oxacyclohexadecan-2-one.

(b) Antihistamines, such as chlorpheniramine maleate, phenindamine tartrate, pyrilamione maleate, doxylamine succinate, and phenyltoloxamine citrate;

(c) Decongestants, such as phenylpherine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine, hydrochloride ephedrine;

(d) Various alkaloids, such as codeine phosphate, codeine sulfate and morphine;

(e) Mineral supplements such as potassium chloride and calcium carbonates, magnesium oxide and other alkali metal and alkaline earth metal salts;

(f) Laxatives, vitamins and antacids;

(g) Ion exchange resins such as cholestyramine;

(h) Anti-cholesterolemic and anti-lipid agents such as gemfibrozil;

(i) Antiarrhythmics such as N-acetyl-procainamide;

(j) Antipyretics such as acetominophen, aspirin and ibuprofen;

(k) Appetite suppressants such as phenylpropanolamine hydrochloride or caffeine; and

(l) Expectorants such as quaifenesin.

Additional useful active medicaments include anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, antimanics, stimulants, gastro-intestinal sedatives, antidiarrheal preparations, anti-anginal drugs, vasodilators, anti-hypertensive drugs, vasoconstrictors and migraine treatments, antibiotics, tranquilizers, antiphychotics, antitumor drugs, anticoagulants and antithrombotic drugs, hypnotics, sedatives, antiemetics, anti-nauseants, anticonvulsants, neuromuscular drugs, hyper- and hypoglycaemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, nutritional additives,

bind certain flavour ingredients, leading to a perceived imbalance of the flavour delivered to the consumer.

By sequestering active agent from the film-forming material in this way, the invention also enables high loading of active agent without causing any deleterious effects on film stability, such as mechanical stability, hygroscopic stability and the like.

Microcapsules may be employed to contain colourants. It has proven to be technically difficult to introduce colours, and in particular, combinations of colours into an edible film without colours leaching out of their assigned configurations during manufacture and during prolonged periods of storage. Employing pre-coloured populations of microcapsules provides a simple means of colouring films effectively, even with intricate designs. Furthermore, because they are encapsulated, the colours display a considerably reduced tendency to leach or diffuse over time. Notwithstanding that colourants may be introduced into the films by means of encapsulation, it is not precluded to add colour to films using conventional means such as over-printing a film using conventional printing techniques.

Finally, microcapsules can be used to added additional visual impact to the edible film of the present invention by using microcapsule populations having different diameters to give an impression of particulate matter in the film.

Microcapsules my comprise up to about 50 wt% of the composition based on dry weight, more particularly 20 to 50% by weight. Active agent loading may be in the range of 10 to 50% by weight of the microcapsules.

All manner of encapsulation technologies may be applied in the present invention. The particular encapsulating medium used will depend upon the nature of the material to be encapsulated, the desired release kinetics and release profile. Apprised of these factors, the skilled person would not have to resort to inventive activity to select a suitable encapsulating medium to achieve a desired result.

Encapsulation techniques suitable in the present invention include spray-drying, complex coacervation, phase separation techniques (both aqueous and organic phase

hydrophilic materials; the combinations of materials being selected to achieve a particularly desired delivery effect, having regard to the active agent.

Particles of active agent may also be coated with encapsulating media of any of the film-forming materials referred to herein above. Coating techniques may be used to coat particles, usually solid particles, of active agent, or even may be used to further coat encapsulated forms described herein above.

Coating may be carried out according to known techniques such as spray coating, pan coating, fluid bed coating, rotogranulator coating, annular jet coating, spinning disk coating, spray cooling, spray drying, filtermat drying, Multi Stage Drying (MSD) drum roll coating, freeze drying, and spray chilling.

The skilled person will appreciate that the particular technique used and the encapsulating material employed will depend upon the nature of the active agent to be encapsulated and the type of release characteristic that is sought to be achieved. For example when a flavouring agent is employed that contains a flavourant aldehyde it is preferred not to employ an encapsulating material that contains a polypeptide such as gelatin, as the aldehyde will act to crosslink the polypeptide over prolonged periods of time and this may effect the films ability to hydrate and dissolve, or disperse rapidly when placed, for example, in the mouth. Furthermore, if food acids are employed in an encapsulating media, the encapsulating media preferably contains fatty substances such as edible waxes, and vegetable fats and the like, or some other medium that efficiently encapsulates acids preventing them from leaching into the film.

The edible film as herein above described may be prepared according to a process comprising the steps of preparing an aqueous solution of the film-forming materials, food acid and other optional excipients or active agents as herein above described; mixing the solution until homogenous, and optionally adding microcapsules comprising active agent, and/or food acid; casting the resultant mixture onto a releasable backing media; coating the mixture, for example using conventional knife-coating techniques; and drying the film.

agent is quickly washed away by saliva. The microcapsules, in contrast, are retained in the oral cavity for longer time periods by being physically trapped in pits or fissures in the oral tissue, or by possessing certain mucoadhesive properties similar to those of the film.

There now follows an Example that serves to illustrate the invention.

Example 1

A formulation containing fruit flavours and food acid was formed according to the following methodology.

	Wet Wt	Dry Wt
Deionised Water	582.7	
Pure Coat 792 Modified Starch	20	20
HPMC	35	35
Gelatin	97	97
Polysorbate 80	10	10
Glycerine	20	20
Sodium Saccharine	5	5
FDC Red 40 Lake	0.3	0.3
Malic acid	50	50
Cherry Emulsion	130	48.1
Cherry Encapsulated	50	50
TOTAL	1000	335.4

A solution was made of the cherry flavourant in water. This solution was mixed with the encapsulating agent (Flavorburst ® Dry Protein Encapsulate (Givaudan)) for 30 minutes. The Flavourant was absorbed into Flavorburst ® after 30 minutes and a dry encapsulated powder was formed.

A solution of starch was made by adding water to the starch and mixing with high shear until a clear solution was formed.

A solution of gelatin was made by heating deionised water to 70 degrees centigrade and adding slowly with stirring fish gelatin. The solution was cooled to 30 degrees.

Claims

1. An edible film composition for delivering an active agent to the oral cavity, the composition comprising a water-dispersible film-forming material selected from a cellulose ether and a starch, and a food acid.
2. A composition according to claim 1 wherein the food acid is selected from the group consisting of citric acid, malic acid, glacial acetic acid, anthranilic acid, tartaric acid, tiglic acid, ascorbic acid, benzoic acid, tannic acid, succinic acid, adipic acid, fumaric acid, lactic acid, and mixtures thereof.
3. A composition according to claim 1 wherein the food acid is present in amounts of at least about 8 wt% based on the dry weight of the composition.
4. A composition according to claim 1 wherein the active agent is selected from a flavourant formulation, a pharmaceutical agent, a nutraceutical agent, or mixtures thereof.
5. A composition according to claim 1 wherein active agent is encapsulated in microcapsules that are dispersed throughout the film.
6. A composition according to claim 5 wherein the microcapsules comprise a first population of microcapsules containing a first active ingredient, and a second population of microcapsules containing a second active ingredient.
7. A composition according to claim 1 additionally comprising gelatin and or pectin.
8. A composition according to claim 1 in the form of thin wafer.
9. A composition according to claim 8 wherein the thin wafer is a monolayer.
10. A composition according to claim 8 having a thickness of 5 to 200 microns.
11. Packaging comprising a plurality of wafers according to claim 8.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CH 03/00739

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 948 430 A (ZERBE HORST GEORG ET AL) 7 September 1999 (1999-09-07) example 1 column 2, line 14 -column 4, line 10	1-4,7-11
X	AU 746 373 B (CREMER K.) 18 April 2002 (2002-04-18) claims; example 1 page 3, last paragraph	1-4,8-11
X	US 4 673 679 A (AUNGST BRUCE J ET AL) 16 June 1987 (1987-06-16) column 9, line 38 -column 10, line 25	1-4,8-11
X	US 2002/131990 A1 (DZIJA MICHAEL R ET AL) 19 September 2002 (2002-09-19) paragraphs '0005!,'0008!,'0012!,'0014!,'0016!-'0018!, '0022!,'0032!-'0037!,'0043!,'0045!,'0056!- '0059! claims; example 6	1-4,7-11
X	EP 0 328 317 A (TAKEDA CHEMICAL INDUSTRIES LTD) 16 August 1989 (1989-08-16) page 2, line 39 -page 3, line 55	1-4,7-11
X	US 5 229 164 A (PINS HEINRICH ET AL) 20 July 1993 (1993-07-20) figures; example 2 column 5, line 39 -column 9, line 28	1-4,7-11
X	EP 0 547 551 A (NAT STARCH CHEM INVEST) 23 June 1993 (1993-06-23) claims; tables III,,VI,X,XI,	1-4,7
A	BRANDT L.: "Cellulose Ethers" , WILEY-VCH , ULLMANN'S ENCYCLOPEDIA OF INDUSTRIAL CHEMISTRY, 6TH ED. XP002268344 page 693 -page 722	
A	KESTR J J ET AL: "EDIBLE FILMS AND COATINGS A REVIEW" FOOD TECHNOLOGY, INSTITUTE OF FOOD TECHNOLOGISTS. CHICAGO, US, December 1986 (1986-12), pages 47-59, XP002912370 ISSN: 0015-6639 the whole document	
A	US 6 419 903 B1 (CURTIS JOHN P ET AL) 16 July 2002 (2002-07-16) column 2, line 20 -column 4, line 49	

International Application No
PCT/CH 03/00739

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5948430 A		ID 22526 A	28-10-1999
		JP 2001504106 T	27-03-2001
		KR 2000053184 A	25-08-2000
		NO 991921 A	22-04-1999
		NZ 335063 A	22-12-2000
		SK 62299 A3	13-03-2000
		TR 9901633 T2	21-09-1999
		TW 533083 B	21-05-2003
		US 2002127190 A1	12-09-2002
		US 2002150544 A1	17-10-2002
		US 6177096 B1	23-01-2001
		US 6284264 B1	04-09-2001
		US 2001046511 A1	29-11-2001
		ZA 9710093 A	25-05-1998
AU 746373 B	18-04-2002	DE 19652268 A1	18-06-1998
		AU 746373 B2	18-04-2002
		AU 5654798 A	15-07-1998
		WO 9826763 A1	25-06-1998
		EP 0959875 A1	01-12-1999
		JP 2001506612 T	22-05-2001
		KR 2000057627 A	25-09-2000
		NO 992944 A	16-06-1999
US 4673679 A	16-06-1987	EP 0250796 A2	07-01-1988
		JP 62277324 A	02-12-1987
US 2002131990 A1	19-09-2002	AU 1778902 A	11-06-2002
		CA 2428445 A1	06-06-2002
		EP 1337148 A2	27-08-2003
		WO 0243657 A2	06-06-2002
EP 0328317 A	16-08-1989	CN 1036967 A	08-11-1989
		EP 0328317 A1	16-08-1989
		JP 1289457 A	21-11-1989
US 5229164 A	20-07-1993	DE 3545090 C1	25-06-1987
		AT 62406 T	15-04-1991
		AU 577213 B2	15-09-1988
		AU 6841687 A	15-07-1987
		CA 1289074 C	17-09-1991
		DE 3678719 D1	16-05-1991
		DK 396787 A ,B,	29-07-1987
		WO 8703805 A1	02-07-1987
		EP 0227050 A1	01-07-1987
		EP 0250578 A1	07-01-1988
		GR 3002266 T3	30-12-1992
		JP 7078018 B	23-08-1995
		JP 63502430 T	14-09-1988
		NO 873105 A ,B,	24-07-1987
EP 0547551 A	23-06-1993	CA 2085457 A1	17-06-1993
		DE 69223024 D1	11-12-1997
		DE 69223024 T2	18-06-1998
		EP 0547551 A1	23-06-1993
		ES 2109303 T3	16-01-1998
		FI 925699 A	17-06-1993
		NO 924821 A	17-06-1993